

REVIEW

Autologous and allogeneic stem cell transplantation for chronic lymphocytic leukemia

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Allogeneic and autologous stem cell transplantation (SCT) are increasingly considered for treatment of patients with chronic lymphocytic leukemia (CLL). In order to assess the potential therapeutic value of SCT for CLL, the present article aims at answering the following crucial questions: (1) Is SCT a curative treatment? (2) Does SCT improve the prognosis of poor-risk CLL? (3) Do risk factors exist which are useful for defining prognostic groups in terms of feasibility and post-transplant outcome? The efficacy of auto-SCT relies exclusively on the cytotoxic therapy administered. To date, there is only limited hope that autotransplantation can cure the disease. Nevertheless, the results of the published series suggest that auto-SCT is capable of improving the prognosis of CLL with poor-risk features. Well defined favorable conditions for successful autografting are the status of the disease (CR or VGPR) and the number of lines of therapy (<2) before transplantation. The crucial anti-leukemic principle of allo-SCT consists in the immune-mediated GVL effects conferred with the graft. The GVL activity explains that allografting seems to be curative for at least a subset of patients. However, as long as allo-SCT in CLL is still associated with an excessively high treatment-related mortality, only selected patients with advanced poor-risk disease should be considered for allografting. The development of conditioning regimens with reduced intensity may allow extending the indications of allogeneic SCT for CLL in the near future.

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Introduction

Despite some progress in therapy, chronic lymphocytic leukemia (CLL) remains incurable with standard treatments. This, coupled with the advanced age of many patients as well as the relatively indolent course of the disease in a substantial proportion of cases, makes symptom palliation a reasonable treatment goal in many cases. Nevertheless, about one-third of the patients are under the age of 60, and 10–15% are younger than 50. In this group of patients, the aim of treatment cannot merely be palliative. Young patients with poor-risk CLL requiring therapy should be offered experimental therapies aimed at achieving cure. For all these reasons, allogeneic and autologous stem cell transplantation (SCT) is increasingly considered for treatment of patients with CLL,¹ the hope being that – as with other hematological malignancies – transplants can cure a fraction of patients. The role of transplants in CLL, however, has not been established in clinical trials, and they should still be considered as experimental procedures in this disease.

In order to assess the potential therapeutic value of SCT for CLL, the present article reviews the most important clinical trials in this field, thereby attempting to answer the following crucial questions for both allo- and auto-SCT: (1) Is SCT a curative treatment? (2) Does SCT improve the dismal prognosis of poor-risk CLL? (3) How, when, and in which subgroup of patients should SCT be performed?

As aggressive treatment modalities such as SCT should be restricted to poor-risk patients, however, the basis of considerations about CLL transplants is the definition of poor-risk disease.

Poor-risk CLL

In recent series, the median survival of patients with CLL is about 10 years. Clinical stages, degree of bone marrow infiltration, and doubling time are the most useful parameters for predicting survival. Cytogenetic abnormalities are also very important prognostic factors.² Thus, patients with del(13q) as a single abnormality have an excellent prognosis (median survival: 133 months), whereas those with del(11q) or del(17p) have poor survival (median survival: 79 and 32 months, respectively). In addition, serum levels of thymidin-kinase, β -2 microglobulin and CD23 also correlate with survival. Recently, different groups reported findings which appear of crucial importance for the understanding of the biology of CLL.^{3,4} These groups have shown that the mutational status of the Ig V gene correlates with different disease subsets. Thus, those patients with unmutated Ig V gene (type I or ‘pre-germinal’ CLL) have a poorer prognosis than those displaying mutated Ig V gene (type II or ‘post-germinal’ CLL). Of note, Ig V mutational status proved to be significant even in patients with stage A. Thus, patients with stage A deriving from naive, pre-germinal B cells had a median survival of 8 years as compared to 25 years in those cases deriving from memory B cells ($P=0.0008$).³ In initial reports, the surface expression of CD38 was reported to correlate with the Ig V gene mutational status (ie CD38⁺ $\geq 30\%$ – unmutated Ig V genes; CD38⁺ $< 30\%$ – mutated Ig V genes), however, such a relationship is not clear-cut.^{4,5} The CD38 expression, however, has prognostic significance in itself.

A number of papers specifically dealing with the prognosis of young patients with CLL have been published, concluding that prognostic factors useful in overall series also discriminate different risk groups among younger patients. In a recently reported series analyzing prognostic factors in younger patients (<56 years old), lymphocyte doubling time and other disease progression features were the only significant parameters predicting survival.⁶

In summary, ‘poor-risk’ patients are those with advanced stage (ie symptomatic disease) and additional adverse biologi-

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cal features, such as short doubling time, high lymphocyte count, and diffuse BM infiltration pattern. In the future, 'classical' prognostic factors are likely to be complemented, if not replaced, by genetic markers such as specific cytogenetic abnormalities and Ig V mutational status, which allow identification of poor-risk patients very early in the course of the disease. As a consequence, patients with both unmutated Ig V genes and adverse interphase cytogenetics might be candidates for aggressive treatment even in asymptomatic stages.⁷

Autologous stem cell transplantation

To date, only four studies on autologous SCT for CLL are available which comprise sufficiently large patient numbers with informative analyses of prognostic factors to allow an approach to these three critical issues: the recent update of the CLL database of the European Group for Blood and Marrow Transplantation (EBMT),⁸ the International Project on CLL Transplants,^{9,10} the second interim analysis of the CLL3 study of the German CLL Study Group (to be published), and the series from Kiel.¹¹

Is auto-SCT a curative treatment?

As summarized in Table 1, all of these four studies are characterized by low treatment-related mortality, on the one hand, and the lack of a plateau in the event- or relapse-free survival curves on the other hand. The fact that patients continue to relapse up to 5 years post transplant indicates that autografting does not result in the cure of CLL.

Another argument against the curative potential of auto-SCT comes from the molecular follow-up of patients from the Kiel series. Allele-specific PCR amplification of the complementary determining region 3 of the IgH gene (ASO-PCR) detected residual disease in at least two follow-up samples in 28 of 35 cases (80%) with specific CDR3 primers available, although more than half of the patients with a positive ASO-PCR had no evidence of disease by consensus primer PCR, flow cytometry, or clinical assessment. Molecular persistence or recurrence of CLL post transplant was not correlated with Binet stage. This implies that complete disease eradication was not possible by this intensive approach in the vast majority of patients even though the Kiel protocol included highly effective tools for *in vivo* and *ex vivo* CLL cell depletion and focused on individuals with early (though poor-risk) disease.¹¹ Similar findings were observed by the Barcelona group. In contrast to allogeneic transplantation, where residual disease

may disappear even months after SCT due to graft-versus-leukemia effects, there is no doubt that in the autologous situation, molecular CLL recurrence is a clear-cut indicator of an imminent clinical relapse.^{12,13} Taken together, there is limited hope that CLL can be cured by standard myeloablative therapy with reinfusion of *ex vivo* B cell-depleted autografts alone.

Does auto-SCT improve the prognosis of patients with CLL?

A reliable evaluation of the impact of SCT on the prognosis of CLL requires prospectively randomized studies comparing autografting with conventional palliative treatment. As such studies are completely lacking to date, the possible prognostic benefit of SCT can only be roughly extrapolated from the results of the published single-arm series. These studies, however, usually suffer from patient heterogeneity and selection bias, and, thus, can hardly be compared with the generally accepted results of conventional therapy.

The most promising series of patients treated with SCT for CLL has been reported by the Dana-Farber Cancer Center. Eighty-one patients with advanced CLL underwent myeloablative therapy including total body irradiation (TBI) and cyclophosphamide followed by reinfusion of autologous BM purged with anti-B cell monoclonal antibodies and complement. There were six treatment-related deaths. With a median follow-up of about 30 months, only 14 patients have relapsed, translating into a projected 4-year disease-free survival of 63%. These figures appear to be clearly superior to any conventional second-line regimen published.¹⁴⁻¹⁷ In the Kiel series, we analyzed 19 patients in whom autografting was attempted as part of a second-line strategy. In these individuals, freedom from treatment failure (FFTF) post mobilization (= SCT attempt) was compared to FFTF after the last conventional regimen prior to mobilization. It became apparent that FFTF after SCT attempt was much longer than after the last standard chemotherapy (median FFTF 10 months vs not reached, $P=0.0002$; Figure 1), implying that SCT allows more efficient tumor control than conventional treatment. Taken together, although the results of the published trials are promising, data illustrating a clear-cut therapeutic benefit of autografting in CLL are still very sparse, and the results of the ongoing prospective studies have to be awaited.^{18,19}

The long-term outcome after autografting may also be influenced by late complications, in particular, secondary malignancies and infections. Due to the impaired function of the lymphoid system, there is an increased risk of viral infections particularly during the first year post transplant.²⁰ How-

Table 1 Autologous SCT in CLL

Trial	EBMT	Int. project	Kiel	GCLLSG
Trial type	registry data, retrospective	registry data, retrospective	single-center prospective	multi-center prospective
n	370	124	77	105
TRM	10%	6% (3 M.)	4%	5%
2y-EFS	na	69%	87%	na
4y-EFS	na	37%	69%	na
2y-OS	82%	83%	94%	88% ^a
4y-OS	69%	65%	94%	na
plateau	no	no	no	no

TRM, treatment-related mortality; 2y-EFS, event-free survival 2 years post SCT; 2y-OS, overall survival 2 years post SCT.

^aSurvival of all patients included 2 years after start of treatment (intent-to-transplant analysis).

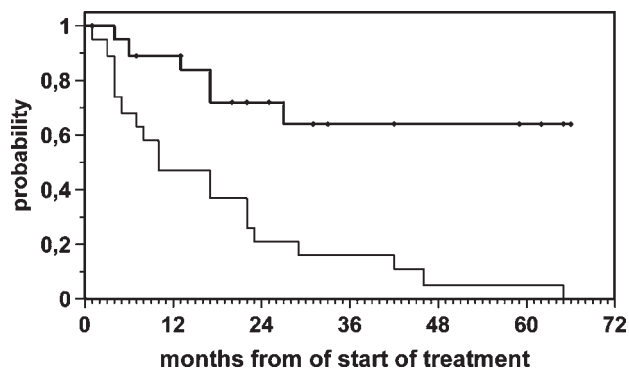


Figure 1 Freedom from treatment failure (FFTF) in the patients who underwent salvage SCT. Thin line, FFTF after the last conventional regimen prior to SCT attempt. Bold line, FFTF after start of high-dose protocol (by intention-to-treat).

ever, infections are rarely life-threatening and thus do not have a discernible effect on overall survival. Secondary neoplasms have turned out to be a critical problem after autologous bone marrow and stem cell transplantation. Information on this particular issue in the CLL setting is sparse. In the Kiel series ($n = 67$), the cumulative incidence of AML/MDS is 6% (95% CI [0;16]) after 5 years and that of all secondary neoplasms 13% (95% CI [1;26]) (unpublished data), which seems comparable to figures reported for other lymphoma.^{21,22}

How, when, and in which subgroup of patients should autologous SCT be performed?

Source of stem cells: Following the general trend in autologous transplantation, peripheral blood is becoming the main source for hematopoietic stem cells. In the EBMT series no differences have been observed between transplants performed from bone marrow and peripheral blood.²³ Fludarabine, especially in heavily pretreated patients, can jeopardize the collection of a sufficient number of peripheral blood progenitor cells.^{24,25} This has led some groups to avoid fludarabine in CLL patients to be included in transplant programs. It should be noted, however, that most patients treated with fludarabine have previously received other lines of therapy – a fact that negatively influences harvesting. The outcome of harvesting after front-line therapy with fludarabine should be prospectively assessed. Preliminary studies failed to demonstrate a significant impairment of stem cell collection in this situation.²⁶ From the practical point of view, it should be noted that an interval of no less than 3 months should be left between the last dose of fludarabine and the leukapheresis, since a shorter interval may be associated with a poor collection of hematopoietic stem cells.²⁴

Conditioning regimen: Although encouraging results have been observed after high-dose chemotherapy alone followed by autologous SCT,²⁷ in the vast majority of published stem cell transplants for CLL the myeloablative regimen contained total body irradiation (TBI). The rationale behind this is that CLL cells – similar to other indolent lymphatic neoplasms – are sensitive to irradiation. A recent analysis of 370 CLL auto-transplants by the EBMT identified TBI as a favorable outcome predictor.⁸ However, this observation might have been biased by other factors, such as the center effect. In other retrospec-

tive analyses, no significant differences in outcome have been observed according to the regimen used.⁹ Thus, the best preparative regimen for autografting patients with CLL is still unknown.

Purging: Several methods of purging, such as B cell-negative selection, CD34⁺-positive selection, or double selection (ie positive selection of CD34 cells followed by B cell-negative selection), are available. All of them can produce a significant degree of B cell depletion of the harvest; this could theoretically diminish the risk of relapse due to the reinfusion of tumoral cells.^{15,28–30} A possible benefit of purging has been observed in one single-center series¹⁵ but not in registry studies,^{8,10} meaning that clear-cut evidence for the usefulness of purging of CLL autografts is still lacking. As long as cure is intended, however, we believe that autotransplantation concepts in patients with CLL should comprise effective purging of PBSC to rule out the possibility that successful disease eradication *in vivo* is counteracted by reinfusion of tumor cells along with the graft.^{12,20} This goal, however, might also be achieved with *in vivo* purging by infusion of monoclonal antibodies during the time of harvesting or autografting.³¹

Purging may retard hematological and immune recovery, which is of concern when considering the already depressed immune status in CLL patients.^{32–34}

Timing of transplant: Although randomized trials addressing the impact of the interval between the diagnosis and the transplant on the outcome of the procedure have not been conducted, some retrospective data suggest a better outcome for patients transplanted in an earlier phase of the disease.^{8,9} This argues in favor of transplanting patients as soon as treatment is indicated. A trial proposed by the EBMT in which patients would be randomized between immediate vs deferred transplantation might contribute to clarify this issue. On the other hand, the case could be made as to whether, rather than transplanted up front, patients should be harvested up front – once a response is obtained, without further delay. The reason for this is that in some studies the most important limitation found with a 'deferred-transplant' policy has been the impossibility to collect enough CD34⁺ cells. The influence of timing and stage on the feasibility of harvesting and achievement of minimal disease prior to SCT has been addressed in the prospective Kiel and GCLLSG trials. In both series, about one-fifth of all patients considered for transplant experienced pretransplant failure, ie lack of a suitable graft or a sufficient response. A history of Binet stage C disease was the predominant factor predicting for poor pretransplant outcome, as illustrated by a failure probability of 36% and 58%, respectively, in the Kiel and CLL3 studies.^{11,19}

In which subgroup of patients should autologous SCT be performed?

In order to identify subgroups of patients who are most likely to benefit from SCT, prognostic factor analyses are needed. Possible explanatory variables predicting for the success of autografting can be divided into two groups: (1) Course-related risk factors are those which develop as the disease continues (eg stage, time from diagnosis, intensity of pre-treatment, timing of transplant). Their prognostic impact may be bypassed by early transplant. (2) Biological risk factors are determined by genuine biological features of the tumor clone and cannot necessarily be eliminated by early timing of trans-

plant (eg disease sensitivity, lymphocyte count, doubling time, cytogenetics, mutational status).

Prognostic factor analyses are available for all four studies mentioned but must still be regarded as preliminary. Their results are listed in Table 2. Data of 124 patients from the 'International Project on Transplants in CLL' have shown that disease status (CR or very good partial response) before transplantation was the most important prognostic factor for survival and disease-free survival (DFS).⁹ Other variables correlated with a longer DFS in the univariate analysis, but not in the multivariate analysis, were the number of previous lines of therapy (≤ 2 vs > 2), response to purine analogs, degree of bone marrow infiltration pretransplant ($\leq 30\%$ vs $> 30\%$ lymphocytes) and a the interval between diagnosis and transplantation (≤ 36 vs > 36 months). Interestingly, classical prognostic factors at diagnosis such as clinical stage or degree of bone marrow involvement did not influence the outcome after transplant. This suggests that, rather than on course-related factors, the success of the transplant depends primarily on the sensitivity of the disease to treatment (which is a biological risk factor). The relationship between disease status at SCT and transplant results has also been found by the EBMT.⁸ In the Kiel and GCLLSG series, respectively, preliminary analysis showed that the biological risk factors high lymphocyte counts, unmutated Ig V status (Kiel), and unfavorable cytogenetics (GCLLSG) were associated with a poor post-transplant outcome by univariate analysis (Table 2).^{35,36} Studies of prognostic factors, however, should be interpreted with caution, given the possible positive bias among patients undergoing transplantation.

In conclusion, biological risk factors, such as disease sensitivity, lymphocyte count and adverse cytogenetics, are associated with an inferior post-transplant outcome, whereas course-related factors, such as stage and the extent of pretreatment, appear to be less important. Taking into account their preliminary character, these analyses suggest that randomized trials on SCT might be best performed in a salvage setting, since the results of conventional second-line treatment in CLL are poor, whereas the outcome after autografting is encouraging and does not appear to be very different between patients with early and advanced disease, respectively. Thus, the possible benefits of SCT will emerge more easily and rapidly if studied as second-line treatment. Whether this, on the other side, questions the justification of further trials on early transplant remains highly debatable. Almost every patient with poor-risk features will progress to a symptomatic stage and,

ultimately, fulfill the criteria for SCT. Delaying high-dose therapy until advanced stage or need for salvage treatment, however, implies that many patients will never receive an autograft due to mobilization failure and resistant disease.

Allogeneic stem cell transplantation

Allogeneic SCT is a treatment approach which is fundamentally different from autologous transplantation, in particular in the context of indolent diseases such as CLL. Whereas efficacy (and complications) of autografting rely exclusively on the cytotoxic therapy administered, the crucial antileukemic principle of allotransplantation appears to be the immune-mediated anti-host activities conferred with the graft (GVL effects). Accordingly, autologous SCT adds nothing else than intensity (and perhaps a radiotherapeutic component) to conventional treatment. For this reason, the mortality of autotransplantation is nowadays only slightly higher than that of intensive conventional chemotherapeutic regimens, but its capacity for complete eradication of resistant CLL clones seems to be limited, too. On the other hand, allogeneic transplantation introduces the entirely different modality of cellular immune therapy, which appears to be responsible for its superior antileukemic activity as well as for its considerably higher toxicity.

Is allo-SCT a curative treatment?

Three registry series on allogeneic SCT for CLL have been published and are summarized in Table 3. In general, allo-SCT in CLL is characterized by a high treatment-related mortality (TRM) on the one hand and a very low relapse incidence on the other hand.^{13,23,37-40} In most studies, the survival curves appear to approach a plateau in the long term, suggesting that allotransplantation may have curative potential in this disease. Moreover, allogeneic transplants can induce sustained complete responses in patients refractory to treatment, including cases resistant to purine analogs; this is again in contrast to results in autologous transplants in which sensitivity of the disease to treatment is a necessary pre-requisite for the success of the procedure. The superior tumor control provided by allografting in comparison to autografting suggests a pronounced susceptibility of CLL to GVL effects.

Another line of evidence for the presence of GVL activity and, thus, curative potential of allografting in CLL comes from

Table 2 Prognostic factor analysis for post-transplant outcome in autologous SCT in CLL

Trial	EBMT	Int. project	Kiel	GCLLSG
Method	Cox analysis	Cox analysis	log rank test	log rank test
Endpoint	relapse incidence	disease-free survival	molecular clonality	molecular clonality
Variables analyzed	age, sex, time from diagnosis, fludarabine treatment, status at SCT, purging, TBI	fludarabine response, time from diagnosis, pretreatment, status at SCT, purging, TBI	age, sex, time from diagnosis, pretreatment, lymphocyte count, mutational status Binet stage	karyotype, time from diagn., pretreatment, lymphocyte count, Binet stage, status at SCT
Favorable variables	CR at SCT, <36 mos from diagn., TBI yes	CR at SCT	lymphocytes <50 G/1 mutated V _H	CR at SCT, karyotype other than del 11q-

TBI, total body irradiation; CR, complete remission.

Table 3 Allogeneic SCT in CLL

Trial	EBMT (23)	Int. project (13)	NMDP (49)	Omaha (38)
Trial type	registry data, retrospective	registry data, retrospective	registry data, retrospective	single-center retrospective
n	134	46	38 ^a	23
TRM	40%	31%	39%	30%
OS	54% (3y)	56% (5y)	51% (2y)	62% (4y)
plateau	yes	yes	too early	yes

TRM treatment-related mortality; OS, overall survival post SCT.

^aUnrelated donors only.

the documented efficacy of donor lymphocyte infusions and the fact that CLL cells persisting after dose-reduced conditioning for allogeneic SCT disappear with the onset of chronic graft-versus-host disease.^{13,41–44}

Does allo-SCT improve the prognosis of patients with CLL?

In spite of the low relapse rate, survival after allo-SCT is significantly lower than after autologous SCT, at least during the first 4 years. The reason for this is the high toxicity associated with allografting for this particular indication. Even in experienced centers, the TRM of allogeneic SCT in patients with CLL is reported to be up to 50% (Table 3). The causes of these detrimental results are not completely clear, but patient age, selection of poor-risk patients with advanced disease and extensive pretreatment, and the CLL-associated incompetence of the immune system may all contribute to the high TRM observed. The recent development of conditioning regimens with reduced intensity may help to improve the tolerability of allo-SCT in CLL without affecting its GVL activities.

How, when, and in which subgroup of patients should allogeneic SCT be performed?

Source of stem cells: The majority of allotransplants have been performed using a family donor. The experience with allogeneic transplantation from unrelated donors (UD) is very limited. In a recent report, Pavletic *et al*⁴⁹ analyzed the results of transplants from UD in 40 patients with CLL reported to the 'National Marrow Donor Program'. The median age was 44 years, ranging from 26 to 57. Twenty patients (50%) were chemorefractory, and 32 (80%) received prior fludarabine. Estimated day 100 survival was 67%. The incidence of grades III–IV acute GVHD was 28%, and extensive chronic GVHD 35%. Out of 33 evaluable patients, 21 (64%) achieved CR and five (15%) PR. The cumulative 3-year incidence of relapse was 13% (95% CI [1;25]). For 33 patients with available relapse data 3-year disease-free survival was 44% (95% CI [26;62]). Eighteen patients are alive with a median follow-up of 3 years (range: 0.3–5.1 years). The median survival was 1.8 years and estimated overall survival at 3 years was 41% (95% CI [24;58]). Although this is a highly selected series, these data are encouraging and suggest that younger patients with refractory disease for whom a family donor is not available might benefit from UD transplant.

Although bone marrow remains the main source, peripheral blood is increasingly being used to obtain stem cells. No com-

parative studies of results with bone marrow vs peripheral blood allotransplants have been reported.

Conditioning regimens and non-myeloablative stem cell transplants: In most centers, standard TBI/cyclophosphamide has been used as conditioning regimen. It should be noted, on the other hand, that since the GVL effect appears to be very active in CLL, the intensity of the conditioning regimen may not be as important as in other diseases. Given this fact on the one hand and the extremely high TRM associated with standard myeloablative conditioning on the other hand, the use of non-myeloablative regimens is particularly appealing in CLL.

The German CLL Study Group has conducted a pilot study using a non-myeloablative conditioning regimen consisting of a combination of fludarabine and cyclophosphamide. Seven patients with symptomatic CLL relapsing after fludarabine or equivalent high-risk features were eligible. GVHD prophylaxis was performed with CsA/short-course MTX or CsA/MMF. PBSC were obtained from HLA-identical donors. As assessed by XY-FISH or STR-PCR, >95% hematopoietic donor chimerism was achieved in all patients (in two only after DLI). Median time to >95% chimerism was 108 (49–202) days. Early non-hematological toxicity was very low. Five patients experienced acute and/or chronic GVHD; in four cases, chronic GVHD was associated with immunologic and molecular clearance of residual disease surviving conditioning chemotherapy. With 12 (9–24) months of follow-up, all patients are alive and progression-free.⁴⁵ Similarly promising findings were observed in other single-center series.^{44,46,47}

The EBMT Chronic Leukemia Working Party collected data on 63 patients who had undergone allogeneic SCT for CLL using dose-reduced conditioning.⁴⁸ The conditioning regimen consisted of low-dose TBI in only 10%, of a combination of fludarabine and TBI in 13%, and of a combination of fludarabine and alkylating agents in 69% of the cases, respectively. The median number of previous chemotherapy regimens was three (0–8). Seventy-seven percent of the patients had received fludarabine prior to transplant. A complete or partial remission (PR) at SCT was present in 60% of patients, whereas 40% had less than PR. ECOG performance was good (0–1) in 82% of patients. In all cases, HLA-identical donors were used (siblings 81%; unrelated 19%). Cumulative TRM was 19% (95% CI [7;30]) after 12 months. Acute GVHD grade II–IV occurred in 32% of patients, whereas the 12-month cumulative incidence of chronic GVHD was 75%. With a median follow-up of 8 (1–30) months, event-free and overall survival (OS) at 12 months were 69% (95% CI [56;82]) and 80% (95% CI [68;91]), respectively. The 12 month probability of relapse

or progression was 16%, with no event occurring later than 4 months post transplant.

Thus, dose-reduced conditioning appears to favorably influence the outcome after allogeneic SCT for CLL by reducing TRM while preserving GVL activity and seems to be a very promising approach for patients with poor-risk CLL.

Timing of transplant and patient selection: Conclusive prognostic factor analyses for identifying subgroups of patients who are most likely to benefit from allogeneic SCT for CLL are not available to date. However, given the high or uncertain TRM still associated with allografting, at the present time allo-SCT in CLL should be restricted to symptomatic patients with very high-risk disease, such as those refractory to treatment, in early relapse after autotransplantation or other unfavorable features such as unfavorable cytogenetics or unmutated IgVH genes. In these subgroups, the considerable risk of TRM should be more than outweighed by the prognostic improvement due to the effective disease control provided by allogeneic SCT.

Conclusions and perspectives

Autologous and allogeneic stem cell transplantation appear to be fundamentally different treatment modalities for patients with CLL. The efficacy of autografting relies exclusively on the cytotoxic therapy administered. With appropriate supportive care, it is safe and can induce long-lasting clinical and molecular remissions. Feasibility of autologous SCT appears to be best early during the course of the disease, but there is only limited hope that autotransplantation can cure the disease even in this favorable subgroup. Nevertheless, the results of the published series suggest that auto-SCT is capable of improving the prognosis of CLL with defined poor-risk features. Since post-transplant outcome does not appear to be very different between patients with first-line and salvage SCT, respectively, randomized trials on auto-SCT might be best performed in a salvage setting, where the results of conventional second-line treatment in CLL are poor, and thus, the possible benefits of SCT will emerge more easily and rapidly. Such a trial has recently started as a combined effort of the EBMT and several European national groups. Given the excellent feasibility of auto-SCT in early (but not in advanced) stages, further refinement of the procedure towards cure by implementing additional modalities, such as monoclonal antibodies, should focus on early patients with biological poor-risk features, such as adverse chromosomal abnormalities and unmutated Ig V_H genes. The recently launched CLL3C trial of the GCLLSG tries to explore this strategy by adding CAMPATH-1H to the myeloablative regimen.

The crucial antileukemic principle of allotransplantation consists of the immune-mediated GVL effects conferred with the graft. The GVL activity should be responsible for the better disease control observed after allografting which seems to be a curative treatment for at least a subset of poor-risk patients. However, as long as allo-SCT in CLL is still associated with an excessively high TRM, only selected patients with advanced poor-risk disease and low probability of successful auto-SCT should be considered for allografting. The development of conditioning regimens with reduced intensity may allow extension of the indications of allogeneic SCT for CLL in the near future. To this end, the German CLL Study Group runs the EBMT-approved CLL3X trial, which studies the fluda-

rabine-based conditioning regimen in patients with very high-risk disease. Other groups are currently undertaking similar projects.

Taken together, autologous transplantation is preferable for patients with early or sensitive disease. Selected patients with advanced poor-risk disease and low probability of successful auto-SCT should be considered for allografting. However, it must be kept in mind that both autologous and allogeneic stem cell transplantation are still experimental procedures which should not be performed outside of approved clinical trials.

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References

- 1 Gratwohl A, Baldomero H. Re: stem cell transplant numbers decline; research continues. *J Natl Cancer Inst* 2001; **93**: 949.
- 2 Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, Döhner K, Bentz M, Lichter P. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med* 2000; **343**: 1910–1916.
- 3 Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V_H genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood* 1999; **94**: 1848–1854.
- 4 Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, Buchbinder A, Budman D, Dittmar K, Kolitz J, Lichtman SM, Schulman P, Vinciguerra VP, Rai KR, Ferrarini M, Chiorazzi N. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood* 1999; **94**: 1840–1847.
- 5 Hamblin M, Orchard JA, Gardiner A, Oscier DG, Davis Z, Stevenson FK. Immunoglobulin V genes and CD38 expression in CLL. *Blood* 2000; **95**: 2455–2457.
- 6 Mauro FR, Foa R, Giannarelli D, Cordone I, Crescenzi S, Pescarmona E, Sala R, Cerretti R, Mandelli F. Clinical characteristics and outcome of young chronic lymphocytic leukemia patients: a single institution study of 204 cases. *Blood* 1999; **94**: 448–454.
- 7 Kroeber A, Seiler T, Leupolt E, Doehner H, Stilgenbauer S. Ig V_H mutated and unmutated B-CLL tumors show distinct genetic aberrations patterns. *Blood* 2000; **96** (Suppl. 1): 835a.
- 8 Dreger P, van Biezen A, Brand R, Esteve J, Gratwohl A, Kimby E, Michallet M, Milligan DW, Niederwieser D. Prognostic factors for survival after autologous stem cell transplantation for chronic lymphocytic leukemia (CLL): the EBMT experience. *Blood* 2000; **96** (Suppl. 1): 482a.
- 9 Montserrat E, Esteve J, Schmitz N, Dreger P, Meloni G, Dearden C, Scime R, Sutton L, Desablens G, Kimby E, Coiffier B, Pavletic ZS, Michallet M, Juliusson G, Besalduch J, Del Potro E, Caballero D. Autologous stem cell transplantation for CLL: analysis of the impact on overall survival in 107 patients from The International Project for CLL/Transplants. *Blood* 1999; **94** (Suppl. 1): 397a.
- 10 Esteve J, Montserrat E, Dreger P, Meloni G, Pavletic S, Catovsky D, Dearden C, Scime R, Sutton L, Desablens B, Kimby E, Coiffier

- B, Brunet S, Sanz MA, Besalduch J, Caballero D, Juliusson G, Conde E, Del Potro E, Schmitz N. Stem cell transplantation (SCT) for chronic lymphocytic leukemia (CLL): outcome and prognostic factors after autologous and allogeneic transplants. *Blood* 2001; **98**: 482a.
- 11 Dreger P, von Neuhoff N, Sonnen R, Kuse R, Seyfarth B, Glass B, Schmitz N. Feasibility and efficacy of early autologous stem cell transplantation for poor-risk CLL. *Blood* 2000; **96**: 483a.
- 12 Esteve J, Villamor N, Colomer D, Cervantes F, Campo E, Carreras E, Montserrat E. Stem cell transplantation for chronic lymphocytic leukemia: different outcome after autologous and allogeneic transplantation and correlation with minimal residual disease status. *Leukemia* 2001; **15**: 445–451.
- 13 Esteve J, Villamor N, Colomer D, Rovira M, Bosch F, Cervantes F, Lopez-Guillermo A, Blade J, Montoto S, Urbano-Ispizua A, Carreras E, Montserrat E. Different significance of minimal residual disease after autologous and allogeneic stem cell transplantation for chronic lymphocytic leukemia: prognostic and therapeutic implications. *Blood* 2001; **98**: 482a.
- 14 Gribben JG, Neuberg D, Soiffer RJ, Fisher DC, Schlossman R, Alyea EP, Kuhlman C, Ritz J, Nadler LM. Autologous versus allogeneic bone marrow transplantation for patients with poor prognosis CLL. *Blood* 1998; **92** (Suppl. 1): 322a.
- 15 Schultze JL, Donovan JW, Gribben JG. Minimal residual disease detection after myeloablative chemotherapy in chronic lymphatic leukemia. *J Mol Med* 1999; **77**: 259–265.
- 16 Michallet M, van Biezen A, Bandini G, Carreras E, Cornelissen J, Dreger P, Einsele H, Gratwohl A, Kimby E, Niederwieser D, Apperley J. Analysis of prognostic factors on the outcome of autologous and allogeneic stem cell transplantation for chronic lymphocytic leukemia. *Blood* 2001; **98**: 859a.
- 17 Gratwohl A, Passweg J, Baldomero H, Hermans J. Blood and marrow transplantation activity in Europe 1996. European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1998; **22**: 227–240.
- 18 Milligan DW, Davies FE, Morgan GJ, Child JA, Catovsky D. Fludarabine followed by stem cell autografting for younger patients with CLL: Preliminary results from the MRC pilot study. *Bone Marrow Transplant* 1999; **23** (Suppl. 1): S53.
- 19 Dreger P, Döhner H, Emmerich B, Kuse R, Hallek M, Flasshove M, Greinix H, Runde V, Schultze W, von Neuhoff N, Schmitz N. A prospective multicenter study on early autologous stem cell transplantation in CLL (CLL3-Study): first interim analysis. *Bone Marrow Transplant* 2000; **25** (Suppl. 1): S9.
- 20 Dreger P, Viehmann K, von Neuhoff N, Krüss D, Glass B, Kneba M, Mitsky P, Jopp P, Rautenberg P, Mills B, Schmitz N. A prospective study of positive/negative *ex vivo* B cell depletion in patients with chronic lymphocytic leukemia. *Exp Hematol* 2000; **28**: 1187–1196.
- 21 Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. *Blood* 1994; **83**: 3780–3786.
- 22 Krishnan A, Bhatia S, Slovak ML, Arber DA, Niland JC, Nadeemane A, Fung H, Bhatia R, Kashyap A, Molina A, O'Donnell MR, Parker PA, Sniecinski I, Snyder DS, Spielberger R, Stein A, Forman SJ. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood* 2000; **95**: 1588–1593.
- 23 Michallet M, Carreras E, Cornelissen JJ, Dreger P, Einsele H, Gratwohl A, Kimby E, Niederwieser D, Apperley J. Allotransplants and autotransplants in CLL. *Bone Marrow Transplant* 1999; **23** (Suppl. 1): S53.
- 24 Michallet M, Thiebaut A, Dreger P, Remes K, Milpied N, Santini G, Hamon M, Björkstrand B, Kimby E, Belhabri A, Tanguy ML, Apperley JF. Peripheral blood stem cell (PBSC) mobilization and transplantation after fludarabine therapy in chronic lymphocytic leukemia (CLL): a report of the European Blood and Marrow Transplantation (EBMT) CLL subcommittee on behalf of the EBMT Chronic Leukemias Working Party. *Br J Haematol* 2000; **108**: 595–601.
- 25 Ketterer N, Salles G, Moullet I, Dumontet C, Eljaafari CA, Tremisi P, Thieblemont C, Durand B, Neidhardt BE, Samaha H, Rigal D, Coiffier B. Factors associated with successful mobilization of peripheral blood progenitor cells in 200 patients with lymphoid malignancies. *Br J Haematol* 1998; **103**: 235–242.
- 26 Flinn IW, Byrd JC, Morrison C, Jamison J, Diehl LF, Murphy T, Piantadosi S, Seifter E, Ambinder RF, Vogelsang G, Grever MR. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. *Blood* 2000; **96**: 71–75.
- 27 Proia A, Mauro F, Capria S, Cimino G, Cordone I, De Fabritiis P, Foa R, Meloni G. Fludarabine therapy followed by unmanipulated PBSCT: a single center experience on 20 CLL patients. *Bone Marrow Transplant* 1999; **23** (Suppl. 1): S54.
- 28 Bensinger W. Should we purge? *Bone Marrow Transplant* 1998; **21**: 113–115.
- 29 Dreger P, Michallet M, Schmitz N. Stem cell transplantation for chronic lymphocytic leukemia: the 1999 perspective. *Ann Oncol* 2000; **11** (Suppl. 1): S49–S54.
- 30 van Besien K, Keralavarma B, Devine S, Stock W. Allogeneic and autologous transplantation for chronic lymphocytic leukemia. *Leukemia* 2001; **15**: 1317–1325.
- 31 Dyer MJ, Kelsey SM, Mackay HJ, Emmett E, Thornton P, Hale G, Waldmann H, Newland AC, Catovsky D. *In vivo* 'purging' of residual disease in CLL with Campath-1H. *Br J Haematol* 1997; **97**: 669–672.
- 32 Holmberg LA, Boeckh M, Hooper H, Leisenring W, Rowley S, Heimfeld S, Press O, Maloney DG, McSweeney P, Corey L, Maziarz RT, Appelbaum FR, Bensinger W. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. *Blood* 1999; **94**: 4029–4035.
- 33 Peggs KS, Ings SJ, Kottaridis PD, Yong K, Williams CD, Goldstone AH, Mackinnon S. Cytomegalovirus infection and disease after autologous CD34-selected peripheral blood stem cell transplantation for multiple myeloma: no evidence of increased incidence based on polymerase-chain-reaction monitoring (letter). *Blood* 2000; **96**: 369–370.
- 34 Schulenburg A, Kalhs P, Worel N, Hocker P, Knobl P, Greinix HT. Immunologic recovery of patients given CD34-selected peripheral blood progenitor cell transplantation for malignant diseases. *Bone Marrow Transplant* 2000; **25**: 223–224.
- 35 Stilgenbauer S, Ritgen M, Bullinger L, Kröber A, Lichter P, Dreger P, Döhner H. Genomic aberrations in the CLL3 trial of the German CLL Study Group: deletion 11q23 identifies patients with molecular disease persistence after autologous high dose therapy. *Blood* 2001; **98**: 763a–764a.
- 36 Lange A, Ritgen M, Brüggemann M, Schmitz N, Kneba M, Dreger P. Unmutated VH gene status retains its adverse prognostic influence after autologous stem cell transplantation for chronic lymphocytic leukemia. *Blood* 2001; **98**: 861a.
- 37 Michallet M, Archimbaud E, Rowlings PA, Bandini G, Horowitz MM, Bortin MM, Atkinson K, Deeg J, Gahrton G, Goldman JM, Jouet J-P, Montserrat E, Rai KR, Rozman C, Speck B, Gratwohl A, Gale RP. HLA-identical sibling bone marrow transplants for chronic lymphocytic leukemia. *Ann Intern Med* 1996; **124**: 311–315.
- 38 Pavletic ZS, Arrowsmith ER, Bierman PJ, Goodman SA, Vose JM, Tarantolo SR, Stein RS, Bociek G, Greer JP, Wu CD, Kollath JP, Weisenburger DD, Kessinger A, Wolff SN, Armitage JO, Bishop MR. Outcome of allogeneic stem cell transplantation for B cell chronic lymphocytic leukemia. *Bone Marrow Transplant* 2000; **25**: 717–722.
- 39 Khouri I, Przepiorka D, van BK, O'Brien S, Palmer JL, Lerner S, Mehra RC, Vriesendorp HM, Andersson BS, Giralt S, Korblyng M, Keating MJ, Champlin RE. Allogeneic blood or marrow transplantation for chronic lymphocytic leukaemia: timing of transplantation and potential effect of fludarabine on acute graft-versus-host disease. *Br J Haematol* 1997; **97**: 466–473.
- 40 Doney KC. Treatment of chronic lymphocytic leukemia with related donor hematopoietic stem cell transplantation. *Blood* 2000; **96** (Suppl. 1): 201a.
- 41 Rondon G, Giralt S, Huh Y, Khouri I, Andersson B, Andreeff M, Champlin R. Graft-versus-leukemia effect after allogeneic bone marrow transplantation for chronic lymphocytic leukemia. *Bone Marrow Transplant* 1996; **18**: 669–672.
- 42 Mattsson J, Uzunel M, Remberger M, Ljungman P, Kimby E, Ringden O, Zetterquist H. Minimal residual disease is common after allogeneic stem cell transplantation in patients with B cell

- chronic lymphocytic leukemia and may be controlled by graft-versus-host disease. *Leukemia* 2000; **14**: 247–254.
- 43 Dreger P, Glass B, Seyfarth B, Humpe A, Claviez A, von Neuhoff N, Suttorp M, Schoch R, Schmitz N. Reduced-intensity allogeneic stem cell transplantation as salvage treatment for patients with indolent lymphoma after failure of autologous SCT. *Bone Marrow Transplant* 2000; **26**: 1361–1362.
- 44 McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, Chauncey TR, Gooley TA, Hegenbart U, Nash RA, Radich J, Wagner JL, Minor S, Appelbaum FR, Bensinger WI, Bryant E, Flowers ME, Georges GE, Grumet FC, Kiem HP, Torok-Storb B, Yu C, Blume KG, Storb RF. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001; **97**: 3390–3400.
- 45 Dreger P, Stilgenbauer S, Truemper L, Humpe A, Glass B, Seyfarth B, von Neuhoff N, Schoch R, Schmitz N, Döhner H. Allogeneic stem cell transplantation for poor-risk CLL using fludarabine/cyclophosphamide (FC) conditioning. *Bone Marrow Transplant* 2001; **27** (Suppl. 1): S37.
- 46 Khouri I, Munsell M, Yajzi S, O'Brien S, Giral S, Körbling M, Ippoliti C, Donato M, Keating M, Champlin R. Comparable survival for nonablative and ablative allogeneic transplantation for chronic lymphocytic leukemia. *Blood* 2000; **96** (Suppl. 1): 205a.
- 47 Schetelig J, Held TK, Bornhäuser M, Thiede C, Ehninger G, Willenbacher W, Kiehl M, Fauser AA, Schwerdtfeger R, Kröger N, Zander A, Beyer J, Neubauer A, Huhn D, Siegert W. Nonmyeloblastic allogeneic stem cell transplantation in chronic lymphocytic leukemia from related and unrelated donors. *Blood* 2000; **96** (Suppl. 1): 200a.
- 48 Dreger P, van Biezen A, Brand R, Hansz J, Corradini P, Finke J, Lambertenghi-Delilieri G, Russell N, Michallet M, Niederwieser D. Allogeneic stem cell transplantation (SCT) for chronic lymphocytic leukemia using intensity-reduced conditioning. An EBMT survey. *Blood* 2001; **98**: 743a.
- 49 Pavletic S, Khouri I, King R, Bierman P, Bishop M, Carsten M, Giral S, Molina A, Montserrat E, Anasetti C. HLA-matched unrelated donor (MUD) bone marrow transplantation for B-cell chronic lymphocytic leukemia (results from the CLL working group, national marrow donor program). *Proc ASCO* 2000; **19**: 4a.